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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/811,162	03/16/2001	Manuela Martins-Green	407E-000500US	5788

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EXAMINER
DEBERRY, REGINA M

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 05/20/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/811,162	MARTINS-GREEN ET AL.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 March 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-86* is/are pending in the application.

4a) Of the above claim(s) *9-18 and 21-86* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-8,19 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-86* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Status of Application, Amendments and/or Claims

The amendment filed 25 March 2002 (Paper No. 10) has been entered in full. Applicant's election with traverse of Group I (claims 1-8, 19 and 20 and SEQ ID Nos 8 and 9) in Paper No. 10 is acknowledged. The traversal is on the grounds that Examiner's requirement for election of a single amino acid sequence within Group I is improper. Applicant further states that the restriction requirement is improper because it restricts subject matter within claims. A rejection under 121 violates the basic right of the Applicant to claim his invention as he chooses.

This is not found persuasive because no rejection has been made under 35 USC 121. Because Applicant is free to claim their invention any way they choose, there will be situations wherein restriction within one claim is proper. A species requirement would not have been proper because Applicant has the option to state on the record that the different species are obvious over each other and such is not true in the instant. Art disclosing chicken chemotactic and angiogenic factor (cCAF), for example, cannot render obvious claims reciting interleukin-8 (IL-8). The two chemokines are structurally and functionally independent and distinct. Furthermore, the SEQ ID Nos in the instant application, which are drawn to different CXC chemokines, are also composed of different coding regions, different sequences, and/or impart structural and functional differences. However, SEQ ID NO:8 and SEQ ID NO:9 were kept together because both SEQ ID Nos are drawn to IL-8. Applicant is reminded that restriction requirements are petitionable, not appealable.

The requirement is still deemed proper and is therefore made FINAL.

Claims 9-18, 21-86 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Group, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 10.

Claim Objections

Claims 6-8 are objected to because of the following informalities: Claims 6-8 encompass non-elected inventions and require amendment to limit to elected invention. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8, 19 and 20 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claims are generally drawn to a polypeptide comprising a chemokine fragment, wherein said chemokine fragment stimulates the differentiation of fibroblasts to myofibroblast, and wherein said polypeptide does not comprise the full-length, wildtype chemokine.

The art acknowledges chemokines as chemoattractants for leukocyte subpopulations, monocytes and NK cells. Furthermore, Applicant has elected SEQ ID NO:8 and SEQ ID NO:9 which corresponds to the protein fragment of CXC chemokine Interleukin 8 (IL-8). However, IL-8 is best known for its ability to attract and activate leukocytes and their potential role as mediators of inflammation. Murdoch *et al.* (Blood 2000, page 3037, 2nd paragraph) states that chemokines such as IL-8 have also been implicated in the regulation of keratinocyte and endothelial cell function, including the stimulation and inhibition of proliferation, angiogenesis, angiostasis and cell migration. Oppenheim (Adv. Exp. Med. Biol. Vol. 351 pages 183-6, 1993) states that IL-8 is a co-mitogen for keratinocytes and GRO/MGSA stimulates melanoma cell lines (page 184 3rd paragraph). Baggiolini (Adv. Exp. Med. Biol. Vol. 351 pages 1-11, 1993) states that chemotactic activity for neutrophils is well documented for IL-8 (pages 2, 3rd paragraph; pages 3, 1st –2nd paragraph). Yet Baggiolini, states that other effects that have been reported such as induction of cell proliferation, chemotaxis of lymphocytes, etc. must be studied beyond the present level of phenomenology. "They must be substantiated with data on receptors and signal transduction and validated with strict controls, using for instance unrelated chemotactic peptides like fMet-Leu-Phe, and chemotactically inactive CXC proteins" (page 6). The specification is not enabled for the instant claims because

the current art does not teach that chemokines or more specifically IL-8 can stimulate the differentiation of fibroblasts to myofibroblasts.

Applicant's assertion that IL-8 has this activity cannot be accepted without supporting evidence. Applicants demonstrate that cCAF stimulates fibroblast to myofibroblastic phenotype (page 74, lines 1-30). However, the instant examples do not support enablement for IL-8 because the chemokines are different structurally and functionally. IL-8 and cCAF may have similar homology but relevant literature reports examples of polypeptide families wherein individual members have distinct, and sometimes even opposite, biological activities. For example, Tischer *et al.* (U.S. Patent 5,194,596) establishes that VEGF (a member of the PDGF, or platelet-derived growth factor, family) is mitogenic for vascular endothelial cells but not for vascular smooth muscle cells, which is opposite to the mitogenic activity of naturally occurring PDGF which is mitogenic for vascular smooth muscle cells but not for vascular endothelial cells (column 2, line 46 to column 3, line 2). Yan *et al.* (Science 2000) establishes that a change in two amino acids in an epithelial morphogen regulates binding to two distinct receptors. Kopchick *et al.* (U.S. Patent 5,350,836) disclose several antagonists of vertebrate growth hormone that differ from naturally occurring growth hormone by a single amino acid (column 2, lines 37-48).

Applicants also demonstrate that cCAF- treated wounds closed faster than control treated wounds. Wounds treated with the N-peptide of cCAF showed accelerated wound closure but less strongly than with the whole cCAF molecule (page 74, lines 4-22). Furthermore, the specification states, that in addition to stimulating

wound closure through the differentiation of myofibroblasts, cCAF may also be acting to increase the stability of new blood vessels in the granulation tissue. CXC chemokines are produced by the endothelial cells and fibroblasts of the connective tissue and promote angiogenesis. These chemokines are known to affect endothelial cell migration, but part of their role in the formation of new blood vessels may be in stimulating fibroblasts to acquire α-SMA and become the smooth muscle cells of the vasculature (page 78, lines 5-15). Based on this, it is unclear how the instant invention "is not angiogenic" (page 4, lines 14-16 and claim 3).

In addition, the specification is not enabled for fragments which are not 100% identical to the N-terminal amino acid sequence. In order to make a sequence variant, for example, with the reasonable assurance that it would have the desirable properties of the invention, the artisan would need to know which regions of the disclosed polypeptide are responsible for the interactions underlying its biological function(s). As is well recognized in the art, any modification (even a "conservative" substitution) to a critical structural region of a protein is likely to significantly alter its functional properties. It is known for nucleic acids as well as proteins, that even a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many cases Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites (see Wells, 1990, Biochemistry 29:8509-8517). Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. Without sufficient

guidance, the changes which can be made in the structure and still maintain sufficient activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue.

Due to the large quantity of experimentation necessary to demonstrate that IL-8 or variants thereof can stimulate the differentiation of fibroblast to myofibroblast, the lack of direction/guidance presented in the specification regarding same, the absence of working examples directed to same, the complex nature of the invention, and the contradictory state of the prior art, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> **The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.**

Claims 6 and 7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 6 and 7 are drawn to a polypeptide wherein the CXC chemokine fragment comprises an amino acid sequence that is at least 70% or 90% (respectively) identical to an N-terminal amino acid sequence of cCAF, IL-8 or MGSA. The claims are indefinite in the recitation of 70% or 90% identical to the N-terminal amino acid sequences because it is unclear what amino acid residues are encompassed in the N-terminal amino acid sequence. The metes and bounds of claims cannot be determined.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (703) 305-6915. The examiner can normally be reached on Mondays-Fridays 8:00 a.m. - 4:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-7939 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

RMD
May 15, 2002

ELIZABETH KEMMERER
PRIMARY EXAMINER